

Exhibit “A”



**FDA U.S. FOOD & DRUG
ADMINISTRATION**

OFFICE OF REGULATORY AFFAIRS
OFFICE OF PHARMACEUTICAL QUALITY OPERATIONS

U.S. Food and Drug Administration
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WARNING LETTER

CMS # 592387

February 11, 2020

VIA UPS Next Day

Anthony P. Tobasso
President and CEO
KVK-Tech, Inc.
110 Terry Drive
Newtown, PA 18940-3427

Dear Mr. Tobasso:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, at KVK-Tech, FEI 3005117563, 110 Terry Drive, from April 9, 2019 to April 16, 2019.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See Title 21 Code of Federal Regulations (CFR), parts 210 and 211 (21 CFR parts 210 and 211).

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

We reviewed your May 7, 2019, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigators observed specific violations including, but not limited to, the following.

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1. Your firm failed to establish and document the accuracy, sensitivity, specificity, and reproducibility of its test methods (21 CFR 211.165(e)).

Your firm failed to properly integrate co-eluting peaks during impurity testing of phentermine HCL capsules, which resulted in your analysis failing to detect out-of-specification (OOS) results for at least one lot of drug product.

You self-identified this problem in 2016. In a deviation report, you wrote that analysts were using “valley to valley methods” and the “reported impurity levels may not reflect the true concentrations found in the drug.” Your firm conducted training on May 24, 2016, reportedly to teach analysts to properly integrate and measure closely co-eluting peaks during impurity analysis of your drugs. Despite this training, in December 2016 your analyst performed valley-to-baseline integration to calculate the area of the peaks for a stability impurity test for Lot 12456A of phentermine HCL capsules. If the appropriate baseline-to-baseline integration had been performed, the test result for the drug product lot would have exceeded the impurity specification limits. This lot remained on the market until it failed 30-month stability impurity testing on June 20, 2017. Your secondary quality review of the December assay also failed to detect the error. Multiple examples of your firm’s failure to properly integrate closely co-eluting peaks were observed during our inspection.

In your response, you claimed that you have opened a corrective action and preventive action (CAPA) plan to determine if an existing method should be adapted, or if you should develop a new method to improve your resolution of the phentermine HCL impurity peaks. In your response, you acknowledged that the integration method you used potentially lowers impurities results reported for unknown impurities for specific retention times, but went on to say “However, there is a low impact associated with this impurities quantification strategy as the failing batches were ultimately recalled from the market, albeit at a potentially later time.”

In your response, you also stated that you plan to re-train your analysts, reviewers and supervisors on closely co-eluting peaks. However, you failed to explain why your previous training did not adequately correct this issue.

FDA reviewed your method, “MOA 026, Finished Product Test Method, Phentermine Hydrochloride Capsules, USP 15 mg”, cleared by your quality unit on October 25, 2019, and we note that an integration example provided in the procedure is inadequate. The example includes incorrect integration parameters that would result in underreported values for impurities, including the potential to mask OOS impurity values. We are concerned that this standard operating procedure (SOP) was cleared by your quality unit five months after you committed to correcting inadequate integration practices in your test methods.

Failure to properly detect and measure impurities, either through inadequate integration or

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inadequate analytical methods, may result in adulterated drug products being released to the market, or remaining on the market when they fail to meet specifications over the labeled shelf-life of the product.

In response to this letter, provide:

- Appropriate methods and procedures that are sufficiently detailed to prevent integration practices that are not scientifically sound.
- Supportive documentation that your laboratory training performed as part of your CAPA is effective.
- The methodology you plan to use for your review of the resolution of all your commercial drug products.
- The methodology you plan to use for your review of the resolution between peaks in the chromatography methods to test all drugs at your facility. You should provide a summary of findings, which includes the methodology applied and acceptance criteria for your review of the high-performance liquid chromatography (HPLC) testing for other products on the market. USP 621, *General Chapter for Chromatography* may provide assistance with maximum ranges for parameters that might be applicable depending on the robustness of the method. Your studies should evaluate method-dependent aspects in all cases and establish appropriately tight ranges that strictly minimize variability and ensure robustness of each individual method.
- A comprehensive, independent third-party assessment of your laboratory practices, procedures, methods, equipment, documentation, and analyst competencies. Based on this review, provide a detailed plan to remediate and evaluate the effectiveness of your laboratory system.

2. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether the batch has already been distributed (21 CFR 211.192).

Your firm failed to adequately investigate foreign particles found in Lot #15315A of methylphenidate oral solution 5mg/5ml during the filling process. You performed an additional filtration step, filtered out the foreign particles, performed visual inspection, and then released the lot. You released this lot without performing an adequate investigation into the origin and nature of the particles and their effect on drug quality. You attributed the particles to shedding from the wipes during equipment cleaning. Per your own procedure, C Policy 0001, *Deviation Management*, you should have completed a deviation report and conducted additional

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investigation steps. We noted several other significant production deviations that were not adequately documented and investigated.

As a result of our inspection and subsequent communication with your firm, you initiated a recall of Lot #15315A of methylphenidate oral solution 5mg/5ml on November 4, 2019.

In your response, you stated you opened deviations for the manufacturing events specifically mentioned on the Form FDA 483. However, you did not commit to conducting a thorough review of all manufacturing events of a similar nature for drug products within expiry. Furthermore, the documentation you provided showed that you planned to take steps to ensure that shedding wipes were not used for this purpose in the future: you examined your reserve samples for evidence of particles, but you failed to provide sufficient evidence to conclude that the particles were from a wipe. In addition, you have not adequately explained why this issue, and other significant issues, were not adequately investigated at the time of occurrence. You also failed to include a copy of the deviation report you opened for this event.

In response to this letter provide:

- A copy of Deviation DEV-2019-0107, including any updates, showing the effectiveness of your corrective actions for Lot #15315A.
 - Scientific data regarding various particulate matter that you have seen in your drug products, including microscopic and chemical analyses
 - A comprehensive, independent assessment of your manufacturing records for the past four years to determine if manufacturing events that should have been the subject of a CAPA were missed. Please summarize the issues found and the appropriate CAPA needed and taken.
-
- A comprehensive, independent assessment of your overall system for investigating deviations, discrepancies, complaints, OOS results, and failures. Provide a detailed action plan to remediate this system. Your action plan should include, but not be limited to, significant improvements in investigation competencies, scope determination, root cause evaluation, CAPA effectiveness, quality assurance unit oversight, and written procedures. Address how your firm will ensure all phases of investigations are appropriately conducted.
3. **Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b)).**

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Data generated from your laboratory testing systems is not adequately protected from deletion or alteration. For example, four of your quality assurance employees had administrator access privileges in Empower 3 chromatographic testing software, which is used for HPLC assay and impurity analysis of finished drug products.

Additionally, data files could be modified or overwritten without being captured on audit trails on your stand-alone laboratory equipment, including your particle size analyzer, atomic absorption spectrophotometer, and Fourier transform infrared spectrophotometer.

During the previous FDA inspection, we notified you that one of your stand-alone pieces of analytical equipment, the inductively coupled plasma mass spectrometry device, did not have adequate controls regarding CGMP data it generated. You opened CAPA 18-072 to address this problem, which included a recommendation to include extending corrective actions to all of your stand-alone laboratory equipment with a due date of February 15, 2019. However, at the time of the April 2019 inspection, you had not implemented corrective actions for all your stand-alone laboratory equipment. You failed to complete your own recommended corrective actions.

In your response, you wrote that you had removed the administrator privileges for the four quality unit employees in the Empower 3 software. You also reported that you opened a CAPA-2019-0007 on March 29, 2019, to require proper configuration of your stand-alone equipment. You stated that you were using a "manual system which complies with 21 CFR Part 211" but you did not provide adequate details of your system and your interim controls. Your response failed to provide adequate supportive documentation to evaluate the effectiveness of your CAPA.

Data Integrity Remediation

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. See FDA's guidance document *Data Integrity and Compliance With Drug CGMP* for guidance on establishing and following CGMP compliant data integrity practices at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/data-integrity-and-compliance-drug-cgmp-questions-and-answers-guidance-industry>.

We strongly recommend that you retain a qualified consultant to assist in your remediation. In response to this letter, provide the following.

- A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include:
- A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude.

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- Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party.
 - An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses.
 - A comprehensive retrospective evaluation of the nature of the testing data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses.
- B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity and analyses of the risks posed by ongoing operations.
- C. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. Your strategy should include:
- A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all the data you generate including analytical data, manufacturing records, and all data submitted to FDA.
 - A comprehensive description of the root causes of your data integrity lapses, including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm.
 - Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring.
 - Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data.
 - A status report for any of the above activities already underway or completed.

Conclusion

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility. You are responsible for investigating and determining the causes of these violations and for preventing their recurrence or the occurrence of other violations.

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If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C. 356C(b). This also allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

Correct the violations cited in this letter promptly. Failure to promptly correct these violations may result in legal action without further notice including, without limitation, seizure and injunction. Unresolved violations in this warning letter may also prevent other Federal agencies from awarding contracts.

FDA may also withhold approval of requests for export certificates and approval of pending new drug applications or supplements listing your facility as a supplier or manufacturer until the above violations are corrected. We may re-inspect to verify that you have completed your corrective actions.

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

Send your electronic reply to orapharm1_responses@fda.hhs.gov. Your written notification should refer to the Warning Letter Number above (CMS # 592387) and your FEI # 3005117563.

If you have any questions, contact Compliance Officer, Lisa Orr, at lisa.orr@fda.hhs.gov or 302-573-6447, extension 109.

Sincerely,

Diana Amador-
toro -S

Digitally signed by Diana Amador-toro -S
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